Changes in Skin Cancer Management

A Personal Perspective

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Changes in Basic Surgical Technique

When I trained as a resident, skin cancer treatment was fairly simple for general dermatologists. Most cases were treated with electrodessication and curettage (ED&C) and occasionally by excision and/or flap and grafting. This was generally because ED&C is quicker than excision and can be incorporated into a busy day of mainly medical dermatology cases. Many dermatologists then concluded that it is better to see more patients, do the treatments on the fly (commonly before biopsy confirmation), and charge less for treatment than to do fewer cases and charge more for each treatment. Bigger cases and recurrences were sent for Mohs micrographic surgery or to ear, nose, and throat specialists; plastic surgeons; or other surgical specialists.

Today, skin cancer patients are no longer exclusively the older, blue-collar workers with a lifetime of sun exposure, wrinkles, and lower expectations of personal appearance. More frequently today, we see business people who regularly play golf or those who have reached levels of ultraviolet (UV) exposure through intentional tanning that had previously been achieved only by outdoor workers. These younger individuals may be more concerned about personal appearances; therefore, cosmetic outcomes have become more important.

More frequently than in the past, dermatologists set aside time specifically for surgery cases. While more time consuming, these cases pay for themselves and add to the variety and satisfaction of dermatology practice. For one thing, dermatologists are better trained and more highly skilled in surgical techniques than was true two decades ago. Patients are sent to plastic surgeons and other surgical specialists for final closure less often these days. Because dermatologists have become more surgically adept, a preponderance of skin cancers are now treated by dermatologists with excision and primary closure with flaps or grafts, as appropriate. This change has also been driven by higher patient expectation of cosmetic outcomes as well as the higher cure rates and improved cosmetic outcomes of good surgical technique.

Medical reasons for these changes include the higher cure rate of excision over ED&C when a knowledgeable eye is picking the margins, and the fact that dermatologists have a better estimate of a cure with a pathology report of clear margins.[1] Changes in surgical technique to date, mainly a shift in emphasis toward more excisional surgery, have been more evolutionary than revolutionary, but even greater changes are coming.

Changes in Radiation Therapy

When my father trained in dermatology, x-ray and Grenz ray treatment were taught in most training programs and were considered a normal part of the dermatologist's armamentarium. This is not the case anymore due to many complex socioeconomic reasons. Radiation therapy is performed in consultation with radiation therapists more commonly now in the United States. When I was a resident, I was taught that radiation therapy was to be used only in those over the age of 40 since the cosmetic and functional outcome of the skin declines slowly with time. Now, I feel that 40 may be too young. I am

more comfortable recommending radiation therapy to those over the age of 70. It is still a useful alternative to extensive reconstruction around delicate areas, such as the eye and nose, but there is still a trend to use it less than in the past. Whether its use has reached a stable low or will decline further with time remains to be seen. Radiation therapy is no longer taught automatically in all training programs, although many programs try to at least familiarize their residents with its potential.

Medical Therapy

Topical 5-fluorouracil (5-FU). Medical therapy for basal cell carcinoma (BCC) with imiquimod is now more competitive with surgery in terms of cure rate than the only previous alternative, topical 5-FU. 5-FU was never a very satisfactory medical therapy for BCC in my view, although it did receive US Food and Drug Administration (FDA) approval for this use when first approved years ago. In my experience, the cure rates with topical 5-FU have generally been less than 50 percent with considerable pain and irritation that usually prevented treatment durations longer than a few weeks. When recurrences occurred, they were more likely to be large, broad-based areas of deep tumor, persisting at a depth beyond effective concentrations of the drug necessary to achieve complete destruction.

The FDA's standards for skin therapies are more stringent now than they were when 5-FU was approved for treating BCC, and it is doubtful that 5-FU would be approved for this purpose if it were going through approval now.

Topical imiquimod. Topical imiquimod is capable of cure rates of at least 85 percent (FDA approval trials) for superficial BCCs. For those of us who have learned to use it more effectively, initial clinical cure rates can exceed 90 percent (applied three times weekly for three months with or without initial curettage for thicker, bulkier lesions).[2] While this is still less effective than surgery, topical imiquimod does provide a reasonable alternative to surgery when the enhanced cosmetic outcome is worth the effort of prolonged medical therapy, particularly for thin nodular and superficial BCCs of the nose, face, upper chest, and back in younger men and women. It currently yields the best possible cosmetic outcome of any cancer therapy commonly available, although intralesional interferon can achieve similar results.

Since this therapy requires more effort and is time-intensive (in terms of the number of visits) than surgery and reimbursed by evaluation and management (E&M) codes rather than surgical codes, it is not popular among physicians. Further expansion of its niche in the panoply of skin cancer management will probably be driven by patient demand unless the reimbursement system shifts dramatically.

Adjuvant immunotherapy with ED&C. Although ED&C is not used as much as in previous decades, combining it with imiquimod immunotherapy used as an adjuvant treatment does two things that may help it make a small resurgence.[3] First, although the effect of adjuvant immunotherapy on surgical cure rates has not been studied prospectively, it likely enhances the cure rate enough to compete favorably with surgical excision with margin checks. Second, the development of scar tissue is suppressed so that there is at least less scar tissue that would occur otherwise, helping to alleviate another objection to this therapy.[4] Curettage without electrodessication, combined with postoperative imiquimod, has also been advocated as an even less scar-provoking therapy.

Either of these approaches is useful in situations where adequate surgical margins and subsequent reconstruction are difficult, particularly around and in the ear, or where the patient is not willing to delay treatment or undergo a lengthy procedure. The cost of imiquimod is a relative inhibition in the use of this therapy, especially when prescription drug coverage is inadequate.

Adjuvant immunotherapy with excisional surgery. Anecdotal evidence suggests that adjuvant immunotherapy with imiquimod is useful in situations where there is a close margin or even a positive superficial margin. In these situations, a postoperative course of the drug from 1 to 3 months can salvage a difficult situation with a complex repair that would otherwise have to be surgically undone. Although modestly risky, the situation may sometimes be salvaged by this use of imiquimod.

Adjuvant immunotherapy with liquid nitrogen. Immunotherapy also seems to be useful in combination with one of our favorite destructive modalities, liquid nitrogen. Liquid nitrogen followed by 1 to 3 months of topical imiquimod for treating thick, precancerous areas or even

early invasive basal or squamous malignancies is a very useful trick when surgery is difficult or impossible due to the number of lesions or the reluctance of the patient to undergo surgery. This strategy was first brought to my attention by Dr. Deborah MacFarlane at MD Anderson Cancer Center. This combination therapy reduces the bulk of the tumor, while the subsequent inflammatory response to the nitrogen kick-starts the imiquimod response by providing target inflammatory cells in the vicinity of the tumor.

New Therapies

Photodynamic therapy (PDT) for tumor therapy. Photodynamic therapy (PDT) is used more commonly in Europe for the treatment of skin cancer. However, its presence in the United States is growing. In the United States, it is primarily used for field treatment of actinic keratoses, although it does have the potential for treating more invasive tumors, such as superficial BCCs and *in-situ* or low-grade squamous cell carcinomas, particularly in combination with other surgical debulking therapies to thin tumor thickness or with imiquimod to enhance immunological effects. PDT's use as a field treatment for actinic keratoses will probably expand, especially because of its favorable financial milieu. PDT will likely be developed further over time for application beyond field therapy of actinic keratoses, depending on the economic factors that have been an important limiting factor for this treatment in the United States in the recent past.

Exploitation of molecular knowledge. A number of drugs have emerged in the last few years that have the potential to fundamentally change skin cancer treatment. These include pathway inhibitors, notably the hedgehog pathway, which is important in maintaining BCCs, and pro-apoptotic drugs, notably the cyclooxygenase (COX) inhibitors.

Basal cell nevus syndrome (BCNS) pathway. Hedgehog pathway inhibitors are currently under study as drug candidates for skin cancer and brain malignancies that require activation of this pathway. One such molecule is a Genentech drug, GDC-0449, which has been tried in skin cancer and advanced medulloblastoma.[1] One anecdotal report suggests that an oral inhibitor of the patched (PTCH) pathway can suppress Gorlin syndrome tumors (BCCs).[5] Whether these drugs become commercial successes remains to be seen. However, the emergence of these new drugs signals that the medical management of skin cancer beyond topical 5-FU and imiquimod may be possible.

Apoptosis stimulators. It has not escaped the notice of the pharmaceutical industry that topical stimulators of apoptosis (programmed cell death) also have potential as drug therapy for skin cancers. Induction of apoptosis is probably a main mechanism for the action of COX-2 inhibitors, such as celecoxib (Celebrex, Pfizer Inc.), which may be an effective chemopreventive agent for skin cancers.[2,3] Clinical use of this or similar drugs for suppression of skin cancer in high-risk patients may follow very soon. Diclofenac (Solaraze, PharmaDerm, A division of Nycomed US Inc., Melville, New York), a topical COX inhibitor indicated for the treatment of actinic keratoses, is already a drug familiar to dermatologists.

Like imiquimod, these drugs and others to come will undoubtedly play some role in our management of skin cancer patients in the future and possibly open new avenues for prevention of skin cancer beyond simple sun protection.

Summary

Even though changes in practice trends for skin cancer therapy are slow, new developments continue, some driven by technology and some driven by socioeconomic factors. Clearly, traditional surgical removal will remain the predominant mode of tumor therapy for the foreseeable future. There will probably be a continued trend of more excision and less ED&C treatment as well as less use of radiation therapy. Medical therapy will likely continue to be used as a surgical alternative, driven by patient demand more than physician choice, but it is doubtful that medical therapy will ever rival surgical technique in terms of numbers in the foreseeable future. Combination therapy with traditional surgery and adjuvant use of medical treatments, such as imiquimod, will likely expand significantly, since it does not threaten any economic considerations and is simply an improvement in outcome over surgery alone.

I feel, as dermatologists, we can look forward to being more involved in the treatment of skin cancer than ever before and to newer drugs and methods of treatment as well as combination therapy, which will give us an even greater ability to tailor treatment to individual patients to achieve

the desired outcome. All of this will make it difficult for us to be replaced by generalists, which is a good thing, both for us and for our patients.

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Dr. Naylor is in private practice in San Antonio, Texas. Disclosure: Dr. Naylor was once a speaker for 3M Pharmaceuticals, the original developer of imiquimod, but currently has no agreements with the pharmaceutical industry, monetary or otherwise.